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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,720	02/26/2004	Margot Mary O'Toole	WYE-030	2740

54623 7590 02/01/2007

KIRKPATRICK & LOCKHART PRESTON GATES ELLIS LLP
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,720	O'TOOLE ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 8, 19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 29, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. This application contains claims that include subject matter drawn to an invention nonelected with traverse in the reply of June 30, 2006. In particular, the claims are inclusive of methods for detecting SFRP1 proteins. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1, 6, 8, 19 and 20 are pending and have been examined herein only to the extent that the claims read on the elected invention of methods for detecting lupus by assaying for SFRP1 nucleic acids.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified in view of Applicants amendments to the claims.

Claims 1, 6, 8, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a) methods for determining an

expression profile in a mouse wherein the methods comprise: i) obtaining a kidney tissue sample from a control, lupus nephritis (LN)- free mouse and a test mouse; ii) determining the level of SFRP1 (SEQ ID NO: 15) mRNA in the control LN-free mouse and in the test mouse; iii) comparing the level of SFRP1 (SEQ ID NO: 15) mRNA in the control LN-free mouse and in the test mouse, and iv) determining that the test mouse has an increased likelihood of having LN if the test mouse has an increase in SFRP1 (SEQ ID NO: 15) mRNA as compared to the control, LN-free mouse, and b) for methods comprising: i) contacting a LN-affected or LN-predisposed mouse kidney cell or mouse with a test agent; ii) determining the level of SFRP1 (SEQ ID NO: 15) mRNA in said kidney cell or in a kidney cell of said mouse; iii) comparing the level of SFRP1 (SEQ ID NO: 15) mRNA in said kidney cell or in said kidney cell of said mouse after said contacting to the level of SFRP1 (SEQ ID NO: 15) mRNA prior to said contacting; and iv) determining that said agent modulates mRNA expression in said kidney cell or said kidney cell of said mouse if there is a decrease in the level of SFRP1 (SEQ ID NO: 15) mRNA after said contacting step as compared to prior to said contacting step, does not reasonably provide enablement for methods for detecting the expression profile of or monitoring the effect of an agent on any SFRP1 gene that is differentially expressed in any pre-symptomatic lupus-affected or predisposed tissue in any human or mouse subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1, 6 ad 8 as amended are drawn to methods for detecting or monitoring lupus comprising the step of detecting SRFP1 expression in a kidney sample, comparing the gene expression profile of a SFRP1 gene in the kidney sample to that of a reference expression profile, and using the comparison to detect or monitor lupus, wherein the kidney sample is obtained from a mouse or human subject. Claims 19 and 20 are drawn to methods comprising contacting a lupus-affected or lupus-predisposed kidney cell or kidney sample from a mouse with an agent, and comparing the expression profile of a SFRP1 gene before and after said contacting step to determine if said agent modulates SFRP1 expression.

The claims as broadly written are not limited to SFRP1 genes of a specific identity or structure. Rather, the claims broadly encompass the detection of any SFRP1 gene that is differentially expressed in any pre-symptomatic lupus-affected or –predisposed kidney tissue. The specification states that the claimed invention is intended to encompass the detection of genes that share an unstated level of sequence identity with the identified genes, homologues of said genes and genes which contain

mutations (insertions, deletions or additions or gross rearrangements) of the identified gene (see, for instance, pages 18, 19 and 21). See also, table 1 of the specification and the disclosure that the cDNA sequence encompasses isoforms and alternative splicing variants of SEQ ID NO: 15. The claimed SFRP1 genes may have functional activities similar to or distinct from the cDNA of SEQ ID NO: 15. Accordingly, the claims are inclusive of methods which detect genes which have distinct biological structural characteristics and activities from the SFRP1 nucleic acids of SEQ ID NO: 15.

Further, claims 1, 6 and 8 include methods which assay for SFRP1 nucleic acids in kidney samples obtained from humans or mice.

Nature of the Invention

The claims encompass methods for detecting an expression profile of a SFRP1 gene in kidney samples as diagnostic of lupus or as a means for screening for agents which modulate SFRP1 expression. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the results of an expression profiling assay in which mRNA levels in kidney tissues from 4 strains of mice were analyzed. The mice strains analyzed were: MRL/MpJ-Fas^{lpr}, MRL/MpJ, C57BL6, and C57BL6/Fas^{lpr}. The phenotypes of these mice are set forth on pages 2-3 of the specification. A comparison of mRNA levels from kidneys of “pre-symptomatic mice” (described in the specification

as including MRL/MpJ mice of 8 weeks or younger) with mRNAs from kidneys of disease-free mice (described in the specification as including C57BL6, and C57BL6/Fas^{lpr} mice) identified mRNAs differentially expressed in pre-symptomatic lupus-affected tissues (see page 69 of the specification). A comparison of mRNA levels from kidney tissues of MRL/MpJ-Fas^{lpr} mice 8 weeks or younger and MRL/MpJ mice 20 weeks or older with C57BL6 and C57BL6/Fas^{lpr} mice (disease-free mice) identified mRNAs differentially expressed in early-stage lupus affected tissues. A comparison of mRNA levels from kidneys of MRL/MpJ-Fas^{lpr} mice 16 weeks or older with C57BL6 and C57BL6/Fas^{lpr} mice (disease-free mice) identified mRNAs differentially expressed in late disease lupus-affected tissues. Table 4 provides a list of 14 genes that are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice. Table 4 also lists 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice. Table 5 lists a number of genes that are under-expressed in lupus-affected kidney tissue as compared to lupus-free kidney tissue of mice.

With respect to the elected invention, the specification teaches that SFRP1 mRNA is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The specification, however, does not teach: (i) the level of expression of homologues, splice variants, or allelic variants of SFRP1 genes or other genes sharing some unstated level of homology with SFRP1 genes in kidney tissues, particularly in kidney tissues from mouse subjects having lupus, or lupus-affected or lupus-

predisposed kidney cells; or (ii) the level of expression of SFRP1, homologues, splice variants, or allelic variants of SFRP1 genes or other genes sharing some unstated level of homology with SFRP1 in kidney tissues from humans, and particularly from kidney samples obtained from lupus affected individuals as compared to normal, control individuals.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between gene expression levels and the occurrence of a disease is highly unpredictable. Knowledge that expression of a gene is associated with a disease such as lupus in one organism (i.e., mice) does not allow one to conclude that expression of this gene is also associated with lupus in other animals, such as humans. In the absence of information regarding the functional properties of the mRNAs and encoded proteins and their role in lupus, it is unpredictable as to whether the SFRP1 gene or other genes sharing homology with SFRP1 will also be differently expressed in humans having lupus as compared to normal, control subjects.

The post-filing date art corroborates the unpredictability of extrapolating the results of gene expression studies performed in one organism to other organisms, such as humans. For example, Coleman (Drug Discovery Today. 2003. 8: 233-235) found that gene expression patterns between mice and humans shared some degree of similarity, but that the basic patterns of gene expression differed and that there was no general rule for predicting gene expression (page 234). Coleman concluded that '(t)he validity of mouse or other animal species as a human surrogate should not be

assumed." These teachings of Coleman support the finding that there is no predictable means for determining whether the gene expression profile obtained in a human will be identical to that in the diverse genus of mammals encompassed by the claims.

Further, Liu et al (Clinical Immunology. 2004. 112: 225-230) studied gene expression in T lymphocytes in human autoimmune disease and murine models of autoimmune disease, including SLE. Liu (see abstract) reported that "we found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models." Only 2 out of 129 genes differentially expressed in human SLE were also found to be differentially expressed in animal models of SLE/autoimmune disease (see page 228).

Additionally, Liu (page 228) reported that while a conserved gene expression profile was detected in lymphocytes of humans with autoimmune disease, the profile was also seen in unaffected first-degree relatives. This finding of Liu further highlights the unpredictability of using the presence or absence of gene expression profiles to diagnose SLE in the general human population and in non-human mammals.

Secondly, while the specification teaches 14 genes, including the mouse SFRP1 gene of SEQ ID NO: 15, which are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice and 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice (see Table 4), this disclosure is not considered to be representative of the broadly claimed genus of any SFRP1 gene. The specification

indicates that "SFRP1" nucleic acids are intended to include a large genus of nucleic acids which differ from the sequence of SEQ ID NO: 15 in that they may contain any number of insertions, deletions or additions in the sequence of SEQ ID NO: 15 (see, for instance, pages 18, 19 and 21). In particular, table 1 of the specification indicates that the recitation of SFRP1 is intended to include isoforms and alternative splicing variants of SEQ ID NO: 15. Accordingly, the claims are inclusive of methods which detect genes which have distinct biological structural characteristics and activities from the SFRP1 nucleic acids of SEQ ID NO: 15. The overall structure and function of the SFRP1 gene to be detected is not defined in the specification or claims. The disclosure of a single mouse SFRP1 gene of SEQ ID NO: 15 whose expression level is associated with lupus is not considered to be representative of the broadly claimed genus of any homologue, mutant, isoform, or splice variant of the SFRP1 gene of SEQ ID NO: 15. The art of identify genes that are associated with a disorder as complex as lupus and using those genes to detect or monitor lupus or to identify agents that could be used to treat lupus is highly unpredictable. The finding that a gene, such as the SFRP1 gene of SEQ ID NO: 15, is over-expressed in mouse models having lupus does not allow one to reasonably predict the structure of other genes that will have similar expression patterns and which could be used to monitor or detect lupus or identify agents for treating lupus.

Working Examples

Again, with respect to the elected invention, the specification teaches that SFRP1 mRNA of SEQ ID NO: 15 is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The specification does not provide any working examples in which expression of homologues, mutants, isoforms or splice variants or any other types of variants of SFRP1 are detected as indicative of lupus or as a means for identifying agents which modulate gene expression.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide sufficient guidance to enable one of skill in the art to extrapolate the findings obtained with mice to humans. There is also insufficient information regarding the functional activity of SLRP1 and the other genes recited in Tables 4 and 5a as it relates to the cause or occurrence of lupus to allow one to conclude that these genes have a similar functional role in contributing to the development of lupus in humans. The teachings of Liu support this unpredictability in that Liu (page 220, column 2) teaches that "(o)ur results indicate that murine models do not perfectly model their corresonding human autoimmune diseases when gene expression profiles are considered. Other investigators have previously recognized limiations of using rodent models to study human diseases."

While methods for expression profiling are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for genes whose expression may linked to a disorder, such as SLE or NL. The results of performing such methodology is highly unpredictable.

Further, the specification does not provide any specific guidance as to how to predictably make and use variants of SFRLP1 or other genes in order to identify additional genes differentially expressed in pre-symptomatic lupus-affected or

predisposed tissues. While one could generate a significantly large genus of nucleic acids in which nucleotides of any identity are added, deleted or substituted within the sequence of SFRLP1, and while one could generate a genus of any nucleic acid from any organism, and then assay each of the nucleic acids to try to determine their biological activity or expression pattern, such trial-by-error experimentation is considered to be undue. Providing methods for searching for additional nucleic acids and trying to determine the function of the resulting nucleic acid or trying to establish an association between the nucleic acids and lupus or other autoimmune diseases is not equivalent to teaching how to make and use specific nucleic acids which are differentially expressed in pre-symptomatic lupus-affected or predisposed tissues.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches an association between the expression of SFRP1 (SEQ ID NO: 15) mRNA levels in kidney tissue samples obtained from mice having a lupus phenotype and in control mice, but does not teach an association between the expression of SFRP1 in humans. The specification also does not teach an association between lupus and altered expression of a representative number of allelic variants, splice variants, homologues, isoforms or other types of variants of SRP1 genes. In view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to arguments:

In the response, Applicants traverse this rejection. Applicants state that the claims have been amended so that claim 1 is limited to humans or mice. It is argued that the Examiner has relied on post-filing date art to show the unpredictability of the art. Applicants assert that while the MPEP acknowledges that post-filing date art may be used to established what would have been known on the filing date or what one of skill in the art would have believed to be predictable on the filing date, it is argued that "none of these exceptions is applicable here. "

This argument has been fully considered but is not persuasive. The post-filing date art of Liu and Coleman are cited to explicitly demonstrate what was known in the art at the time the invention was made. In particular, at the time the invention was made,

it was more than well known in the art that the expression data results obtained with one organism could not be predictably extrapolated to other organisms. Thereby, Liu and Coleman are cited only to verity what was already known and acknowledged in the prior art. Applicants fail to provide any evidence to substantiate their claim that it was predictable in the art at the time the invention was made to extrapolate gene expression data from one mice to humans in order to allow for the diagnose of lupus in humans. Additionally, it is noted that the Coleman reference was available online on February 28, 2003, whereas Applicants claim the benefit of priority to provisional application 60/449,693 filed February 26, 2003. Since the findings of Coleman are based on a review of published references, the teachings of Coleman are considered to represent an overview of what was known in the art at the time the invention was made.

Applicants argue that Coleman finds a certain degree of predictability in the comparison of human and mouse gene expression patterns. It is asserted that Coleman was "unsurprised by this predictability, likely evidencing the expectation of one of ordinary skill in the art as of the February 2003 effective filing date of this application."

This argument has also been fully considered but is not persuasive. Applicants provide no evidence to support their allegation that Coleman evidences the predictability of the presently claimed invention. Contrary to Applicants assertions, Coleman does in fact acknowledge the high level of unpredictability in the art of extrapolating expression data results from one mice to humans. While Coleman acknowledges that some genes may share similar expression patterns, Coleman cautions that "experimental animals are surrogates and the results obtained should not necessarily be taken at face value"

(page 233, col. 1). Coleman also teaches that while "mice and humans are apparently at least 95% identical at the genomic level, this does not prevent our respective phenotypes from being different" (page 233, col. 2). Coleman exemplifies the unpredictability of extrapolating gene expression results obtained in mice to humans by citing the findings obtained with CFTR gene expression. The reference teaches CFTR is predominantly expressed in human salivary and lung, consistent with its functional role of being a transporter in these tissues. On the other hand, in mice expression in the salivary gland and lung is relatively low. In contrast, CFTR expression is relatively high in mice thyroid, uterus and ovary, and relatively low in human thyroid, uterus and ovary. It is also again pointed out that Liu teaches that "we have found very little overlap in the gene expression profile between human autoimmune disease and murine models of autoimmune disease and between different murine autoimmune models" (see abstract). The unpredictability in the art of extrapolating the results obtained in mice to humans is particularly relevant to the present invention wherein the role of SFRP1 gene expression in the occurrence of lupus is not well understood. Without any information regarding the level of SFRP1 gene expression in human kidney tissues and in the absence of any information regarding a functional role for SFRP1 in lupus, it is maintained that it is highly unpredictable as to whether the level of expression of SFRP1 in kidneys can be used in order to diagnose or monitor lupus in humans.

Applicants state that the USPTO has indicated that "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials." Applicants statement and reference to a requirement for human clinical

trials mischaracterizes the Office action. The Office action DID NOT require that Applicants provide data from human clinical trials. Given that the claims are drawn to methods for diagnosing lupus, it is unclear as to how the concept of human clinical trials is relevant to the present invention. An analysis of SFRP1 gene expression in human tissues would clearly not require one to perform human clinical trials. Regardless, to be fully clear to Applicants, there is NO requirement to provide data from a human clinical trial.

The response further asserts that claims 19 and 20 have been amended to recite "mouse," "kidney cells" or "kidney samples," "SFRP1' and "lupus." Thereby, Applicants conclude that the scope of claims 19 and 20 bears a reasonable correlation to the scope of enablement.

Applicants arguments and amendments to the claims have been fully considered but are not persuasive. The claims are not in fact limited to specific mouse and human SFRP1 genes. As set forth in the specification, the recitation in the specification and claims of "SFRP1" is intended to encompass any allelic variant, splice variant, or other mutant of the SFRP1 gene. For instance, in Table 1 of the specification, it is disclosed that the term SFRP1 includes isoforms and alternative splice variants of SEQ ID NO: 15. At page 18 of the specification (paragraph [0074]), it is stated that "LRG" (i.e., SFRP1) polymorphisms may be detected as indicative of a subject's susceptibility to lupus. At page 19, paragraph [0079] –[0080], it is stated that the invention intends to include polynucleotides encoding an LRPP (i.e., SFRP1) or any fragment or mutant thereof. It is also stated that any mutant of SFRP1 includes polynucleotides that

hybridize under reduced stringency conditions. At page 21, paragraph [0081] of the specification, it is stated that an LRG polynucleotide (i.e., SFRP1) may differ from the original LRG by one or more substitutions, additions and/or deletions. For instance, the variant can have up to 25 or more nucleotide additions, additions or deletions and may include an in-frame mutation. The polynucleotide may also have activity that is reduced or enhanced by 50% as compared to the original activity.

However, the specification does not disclose a representative number of variants having any number of additions, deletions, and/or insertions, or other isoforms or splice variants of SFRP1. Accordingly, the disclosure in the specification and prior art of the wildtype mouse cDNA of SEQ ID NO: 15 and of a wildtype SFRP1 cDNA obtained from humans is not representative of the broadly claimed genus of SFRP1 nucleic acids. In view of the unpredictability in the art and lack of specific guidance provided in the specification as to how to make and use variants of SFRP1, it is maintained that the specification has not enabled one of skill in the art to practice the broadly claimed invention.

4. Claims 1, 6, 8, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The following rejection has been modified in view of Applicants amendments to the claims.

Claims 1, 6 and 8 are drawn to methods for detecting an expression profile of a gene in a biological sample comprising the step of comparing the gene expression profile of a SFRP1 gene in a kidney sample to that of a reference expression profile obtained from a human or mouse subject. Claims 19 and 20 are drawn to methods comprising contacting a lupus-affected or lupus-predisposed kidney cell from a mouse or contacting a mouse subject with an agent, and comparing the expression profile of a SFRP1 gene before and after said contacting step.

The specification teaches the results of an expression profiling assay in which mRNA levels in kidney tissues from 4 strains of mice were analyzed. Table 4 provides a list of 14 genes that are over-expressed in kidney tissues from "pre-symptomatic" "early disease" and "late disease" mice, as compared to lupus-free mice. Table 4 also lists 11 genes that are over-expressed in "pre-symptomatic" and "early disease", as compared to lupus-free mice. Table 5 lists a number of genes that are under-expressed in lupus-affected kidney tissue as compared to lupus-free kidney tissue of mice. In particular, the specification teaches that SFRP1 mRNA is increased in kidney tissue from "pre-symptomatic" "early disease" and "late disease" mice as compared to lupus-free mice.

The SEQ ID Nos. for nineteen of the genes differentially expressed in the mouse lupus model are set forth in Table 1. Accordingly, methods for detecting the SFRP1 gene of SEQ ID NO: 15 meet the written description requirement.

However, the claims as broadly written are not limited to SFRP1 genes of a specific identity or structure. Rather, the claims broadly encompass the detection of any

SFRP1 gene that is differentially expressed in any pre-symptomatic lupus-affected or – predisposed kidney tissue.

The specification indicates that the claimed invention is intended to encompass the detection of genes that share an unstated level of sequence identity with the identified genes, homologues of said genes and genes which contain mutations (insertions, deletions or additions or gross rearrangements) of the identified gene (see, for instance, pages 18, 19 and 21). See also, table 1 of the specification and the disclosure that the cDNA sequence encompasses isoforms and alternative splicing variants of SEQ ID NO: 15. The claimed SFRP1 genes may have functional activities similar to or distinct from the cDNA of SEQ ID NO: 15.

. Accordingly, the claims are inclusive of methods which detect genes which have distinct biological structural characteristics and activities from the SFRP1 nucleic acids of SEQ ID NO: 15.

The general knowledge in the art concerning homologues, mutants, allelic and splice variants does not provide any indication of how modification of the sequence of SEQ ID NO: 15 will effect the functional properties of SEQ ID NO: 15. The structure and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of one molecule – i.e., SEQ ID NO: 15 is not representative of the broadly claimed genus of homologues, splice, mutant and allelic variants of SEQ ID NO: 15. A general statement in the specification of a desire to obtain gene sequences, homologues from other species, mutated species, SNPs, polymorphic sequences, novel gene sequences is not equivalent to providing a clear

and complete description of specific sequences which fall within the claimed genus of genes.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Additionally, Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because the claims define the genes only in

terms of their functional properties (i.e., expression properties), one of skill in the art cannot envision the detailed chemical structure of the genes encompassed by the claimed methods, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided in the specification is not deemed sufficient to reasonably convey to one of skill in the art that Applicants were in possession of the claimed genus of any SFRP1 gene that is differentially expressed in any mouse or kidney sample or any lupus-affected or lupus-predisposed mouse kidney sample. Therefore, the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to arguments:

In the response, Applicants traverse this rejection. The response states that it is clear from the specification that one would detect the mouse SFRP1 gene in mouse cells and the human SFRP1 in human cells. Applicants assert that because the mouse and human SFRP1 genes were known at the time the invention was made, naming the

SFRP1 gene provides a sufficiently detailed and relevant identifying characteristic providing evidence that Applicants were in possession of the claimed invention.

This argument has been fully considered but is not persuasive. The claims are not in fact limited to the mouse and human SFRP1 genes which were known at the time the invention was made. As clearly set forth in the specification, Applicants do not intend to limit their claims to the previously disclosed wildtype SFRP1 genes obtained from mice and humans. Rather, the claims are intended to encompass any allelic variant, splice variant, or other mutant of the SFRP1 gene. For instance, at page 9 (Table 1) of the specification, it is disclosed that the term SFRP1 includes isoforms and alternative splice variants. At page 18 of the specification (paragraph [0074]), it is stated that "LRG" (i.e., SFRP1) polymorphisms may be detected as indicative of a subject's susceptibility to lupus. At page 19, paragraph [0079] –[0080], it is stated that the invention intends to include polynucleotides encoding an LRPP (i.e., SFRP1) or any fragment or mutant thereof. It is also stated that any mutant of SFRP1 includes polynucleotides that hybridize under reduced stringency conditions. At page 21, paragraph [0081] of the specification, it is stated that an LRG polynucleotide (i.e., SFRP1) may differ from the original LRG by one or more substitutions, additions and/or deletions. For instance, the variant can have up to 25 or more nucleotide additions, additions or deletions and may include an in-frame mutation. The polynucleotide may also have activity that is reduced or enhanced by 50% as compared to the original activity.

However, the specification does not disclose a representative number of variants having any number of additions, deletions, and/or insertions, or other isoforms or splice variants of SFRP1. Accordingly, the disclosure in the specification and prior art of the wildtype mouse cDNA of SEQ ID NO: 15 and of a wildtype SFRP1 cDNA obtained from humans is not representative of the broadly claimed genus of SFRP1 nucleic acids. Thereby, it is maintained that the specification is not deemed sufficient to reasonably convey to one of skill in the art that Applicants were in possession of the claimed genus of any SFRP1 gene that is differentially expressed in any mouse or kidney sample or any lupus-affected or lupus-predisposed mouse kidney sample.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 are indefinite over the recitations of "lupus-affected" and "lupus-predisposed" mouse kidney cells and mice. It is unclear as to whether a predisposed cell or mouse is limited to a cell from a particular mouse predisposed to developing lupus (i.e., a mouse cell line or strain that develops lupus) or if a predisposed kidney cell or mouse is any cell or mouse that could be affected by lupus – i.e., potentially any kidney cell or mouse. Similarly, it is unclear as whether lupus-affected kidney cells include any cells obtained from a mouse that has lupus, or refers only to kidney cells or mice that have particular morphological or symptomatic signs of

disease in the kidney cells that is characteristic of lupus, or if this phrase is intended to include kidney cells from any mouse (including control mice) wherein it is a property of the kidney cells or mice that they would be affected by the occurrence of lupus or early-stages of lupus. For example, it is unclear as to whether a lupus-affected mouse has lupus and it is unclear as to whether a lupus-predisposed mouse constitutes any mouse since any mouse could in fact eventually develop lupus. The specification and claims do not set forth how one would distinguish a lupus-affected or lupus-predisposed kidney cell from any other mouse kidney cell and how one would distinguish a lupus-predisposed mouse from any other mouse.

Response to arguments

In the response, Applicants state that the claims have been amended to refer to kidney cells and to lupus-affected and predisposed cells and mice. It is stated that the phrases "lupus-affected" and "lupus-predisposed" are definite.

Applicants arguments and amendments to the claims have been fully considered but are not persuasive. As discussed above, it is maintained that the phrases "lupus-affected" and "lupus-predisposed" render the claims indefinite. The specification does not clearly defined these phrases and there is no art recognized definition for these phrases. It remains unclear as to how one would distinguish a lupus-affected or lupus-predisposed kidney cell from any other mouse kidney cell and how one would distinguish a lupus-affected or lupus-predisposed mouse from any other mouse. Accordingly, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Carla Myers

Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER